REMARKS

I. Status of the Claims

Claims 1-5, 10 and 11 are currently pending. Upon entry of this amendment, claims 1-5 are amended without prejudice or disclaimer. Applicants reserve the right to reintroduce the unamended claims in this or another application. New claims 21 and 22 are introduced upon entry of this amendment. Claims 1-5, 10-11 and 21-22 are thus pending following entry of this amendment.

The amended and new claims are supported throughout the specification, including, for example, the following sections:

Claims 1-2:	Paragraph 143
Claim 4:	Paragraph 127
Claims 21 and 22:	Paragraphs 153-154

II. Objections to the Specification:

The title has been amended to more accurately reflect the currently claimed invention.

The cross-reference to related application section has been amended to indicate the status of the priority applications as requested.

III. Objections to the Claims:

The claims have been amended to recite only to the elected sequence, namely SEQ ID NO:1.

IV. Claim Rejections under 35 U.S.C. 112

Claims 1 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, because the reference to "stringent conditions" is said to render the claims indefinite. In response, it is noted that claim 1 has been amended to recite that the polynucleotide comprises a nucleic acid

segment or its complement, wherein said nucleic acid segment hybridizes to at least 750 contiguous nucleotides of SEQ ID NO:1 at 5 °C to 25 °C below Tm in aqueous solution at 1 M NaCl, thereby defining explicitly what is meant by "stringent conditions." This amendment is supported, for example, in paragraph 143.

V. Claim Rejections under 35 U.S.C. §101 and 35 U.S.C. 112, First Paragraph

Claims 1-5, 10 and 11 are rejected under 35 U.S.C. §101 because the claimed nucleic acids are said not to be supported by either a specific and substantial asserted utility or a well established utility. The Office also concludes that the specification fails to teach how to use the claimed nucleic acids and thus also rejects these claims under 35 U.S.C. 112, first paragraph.

The process for evaluating whether the utility requirement of 35 U.S.C. §101 involves first assessing whether the application includes any assertion of utility for the invention. If the application includes such an assertion, then a determination is made whether the assertion identifies a substantial utility. Assuming a substantial utility is identified, then the final step is to evaluate whether the assertion of a specific and substantial utility is credible. If a specific and substantial utility are asserted and it would be credible to one of ordinary skill in the art, then the utility requirement is satisfied (see, e.g., MPEP 2107.02; see also Revised Utility Guideline Training Materials ("Guidelines")). If multiple utilities are asserted, it is sufficient that only one of the asserted utilities satisfy the foregoing three requirements (see, e.g., MPEP 2107.02, and *Raytheon v. Roper* 724 F.2d 951,958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied* 469 U.S. 835 (1984)).

A. The Currently Claimed Invention has a Specific Utility

A specific utility is defined as a utility other than a general utility that is applicable to the broad class of invention. For instance, an assertion that a claimed nucleic acid is useful as a probe to identify larger nucleic acids is, without more, simply a general utility because this is a utility common to the general class of nucleic acids and, as such, does not satisfy the requirement for a specific utility. A statement that an invention has use in diagnosing

an unspecified disease is also considered insufficient without a disclosure of what condition can be diagnosed.

The asserted utilities of the presently claimed nucleic acids, however, are specific and are distinct from the two general utilities just listed. The application, for instance, states that the currently claimed nucleic acids play a role in retinal adhesion and as such are associated with certain ocular disorders such as retinal detachment, chorioretinal degeneration and macular degeneration (see, e.g., paragraphs 31, 85, 89, 229 and 233). The application thus indicates that the nucleic acids can be used in the diagnosis and treatment of such disorders (see, e.g., pages 41-51). Moreover, the application describes a second utility, namely the use of the nucleic acids in nucleic acid arrays. The specification notes that arrays including the presently claimed polynucleotides can be used in a variety of applications including, for instance, expression monitoring, comparison of expression profiles, diagnosis of disease states (see, e.g., those listed above) and to characterize cellular responses to drugs (see, e.g., paragraph 90).

The foregoing asserted utilities are clearly not simply general utilities that are common to all nucleic acids. Rather the asserted utilities are specific to a certain class of polynucleotides. Moreover, although not required, the application describes multiple specific utilities. The specification thus satisfies the requirement that it include an assertion of a specific utility.

B. The Currently Claimed Invention has a Substantial Utility

A substantial utility is defined as one that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Examples of asserted utilities that fail to establish a "real world" context of use include: (1) basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved, and (2) a method of treating an unspecified disease or condition (see, e.g., Guidelines)..

Here the application does more than simply provide a description of general properties that are associated with the claimed nucleic acids. Instead, as noted above, the application concludes that the on the basis of certain sequence characteristics (see below) that the

nucleic acids encode proteins that are important in retinal adhesion and thus associated with ocular disorders such as retinal detachment, chorioretinal degeneration and macular degeneration. As such, the application states that the nucleic acids can be used in the diagnosis and treatment of such disorders. These clearly are "real world utilities" and more than simply a description of properties of the claimed product or a method of treating an unspecified disease. The stated use of the presently claimed polynucleotides in nucleic acid arrays constitutes another "real world" utility because nucleic acid arrays constitute a class of biochemical products. For all the foregoing reasons, the application sets forth multiple substantial utilities.

C. The Asserted Utilities are Credible

In view of the foregoing analysis, the only remaining issue is whether the asserted specific and substantial utilities would be deemed credible to one of ordinary skill in the art. The Office Action concludes that the utility is not credible for primarily two reasons, asserting: (1) that the specification fails to demonstrate "a causal correlation or nexus of the claimed poly[nucleotide] with any of the conditions or disorders contemplated by the instant specification" (Office Action at page 6), and (2) that there is "absolutely no evidence of record or any line of reasoning that would support a conclusion that the 'IPM 150' protein of the instant application could be used in methods of diagnosis, treatment or amelioration and/or prevention of disease" (Office Action at page 5). These assertions are addressed in turn.

With respect to the alleged failure to establish a "causal correlation or nexus" with the asserted utilities, Applicants submit that the Office is applying an incorrect standard for evaluating whether the utility is credible. The law does not require establishment of a "causal correlation" for an assertion of diagnostic or therapeutic utility to be deemed credible. The MPEP, for instance, states that to establish a credible utility, an Applicant does not "have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt'" (MPEP 2107.02; see also *In re Irons*, 340 F.2d 974,978, 144 USPQ 351, 354 (CCPA 1956)). Rather a utility is deemed credible "if there is a reasonable correlation between the activity in question and the asserted utility" (MPEP 2107.02; emphasis in original. See also

Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985)). As described in greater detail below, Applicants submit that the application does in fact establish a "reasonable correlation" between the asserted activity and stated utility. This is sufficient to satisfy the credibility prong of the utility analysis.

Furthermore, the MPEP emphasizes that in most cases an applicant's assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. 101 (see, e.g., MPEP 2107.02). The MPEP also points out that utility rejections have rarely been sustained by the federal courts, usually only being sustained if (1) the applicant failed to disclose any utility, (2) the utility could only be true if it violated a scientific principle, or (3) the asserted utility was wholly inconsistent with contemporary knowledge in the art. (MPEP 2107.02; emphasis in original). Here, Applicants have not failed to assert a utility (see above), nor is it the case that the asserted utility could only be true if it violated a scientific principle. Finally, as described below, nor is the asserted utility "wholly inconsistent" with contemporary knowledge in the art. It is thus submitted that when the appropriate standard is applied that the utilities asserted in the application are credible.

Applicants also respectfully disagree with the assertion that the specification is devoid of any evidence or reasoning that supports the use of the currently claimed nucleic acids in the diagnosis and/or treatment of certain ocular disorders such as retinal detachment, chorioretinal degeneration and/or macular degeneration. It is instead submitted that the application provides a well reasoned analysis that is sufficient to allow one of ordinary skill in the art conclude that there is a reasonable correlation between the role of the proteins encoded by the claimed nucleic acids and the asserted diagnostic and/or therapeutic utilities.

The specification, for example, begins by stating that the relationship between the retina and choroid is crucial to eye function and that many diseases, including various retinal and chorioretinal degenerations and macular degeneration, result when this relationship is compromised (see, e.g., paragraph 14). The specification then notes that the interphotoreceptor matrix (IPM) occupies the space between the retina and choroid, thus indicating that the molecules in this region are likely important in maintaining the relationship between the retina and choroid (see, e.g., paragraph 16). The IPM is also important because it has been shown in a

variety of studies to play a critical role in maintenance of retinal photoreceptor cells; IPM proteoglycans have also been shown to mediate photoreceptor cell adhesion (see, e.g., paragraph 16). Moreover, the IPM includes cone matrix sheaths. A number of studies have implicated the proteoglycans associated with cone matrix sheaths in proper retinal adhesion. The specification thus concludes that the specific components of the IPM act as major adhesive elements bridging the retinal pigmented epithelium (RPE)-retina interface (see, e.g., paragraph 18). In support of this conclusion, the specification points out that the results of a number of studies indicate a correlation between changes in IPM composition and the etiology of photoreceptor demise in certain ocular degenerations (see, e.g. paragraph 21).

The results described in the specification are consistent with the conclusion that the currently claimed nucleic acids, which are expressed in the IPM, encode proteins (e.g., proteoglycans) that play a role as an adhesive element that bridges the RPE-retina interface, thus making the nucleic acids useful in the diagnosis and/or treatment of various ocular disorders (e.g., retinal detachment, chorioretinal degeneration and/or macular degeneration).

The specification states, for instance, that the claimed nucleic acids, include consensus sequences for N-linked glycosylation and an additional four probable consensus sequences in the carboxy terminus. There are also 16 sites in the central domain region for O-linked glycosylation (see, e.g., paragraph 78). The evidence thus indicates that the currently claimed nucleic acids encode proteins with numerous glycosylation sites. As noted above, IPM proteoglycans have been shown to mediate photoreceptor cell adhesion (see, e.g., paragraph 16).

It is also noted in the specification that hyaluronan has been demonstrated to be a component of the IPM and that hyaluronidase disrupts cone matrix sheaths in vitro and weakens retinal adhesion in vivo. The N-terminus of IPM 150 includes hyaluronan binding domains in the N-terminus (see, e.g., paragraph 80). This evidence is consistent with the conclusion that IPM 150 can play a role in retinal adhesion through interaction with hyaluronan (see, e.g., *Id.*).

The specification further notes that the core protein encoded by IPM 150 does not possess any hydrophobic regions that would constitute transmembrane domains, thus indicating that the protein is secreted into the interphotoreceptor space rather than being incorporated into a membrane (see, e.g., paragraph 81). In view of extensive earlier reports showing a role for IPM

proteoglycans in adhesion of the neural retina to the RPE (see references cited in paragraph 81), the specification concludes that that IPM 150 can act as a bridge between membrane-associated molecules on the photoreceptor and RPE cell surfaces to achieve retinal adhesion (*Id.*).

Finally, the specification states that the distribution of several cysteine residues at the amino and carboxyl-terminal regions is consistent with EGF-domains, which are present in many extracellular proteins and correlated with cell survival. The specification thus concludes that IPM 150 can have a role in promoting photoreceptor viability, a conclusion that is consistent with a number of previous studies indicating that proteoglycans in the IPM are important in maintaining photoreceptor cell viability (see, e.g., paragraph 79).

Thus, contrary to the conclusion reached in the Office Action, the specification does provide a detailed description that is consistent with the asserted utilities. Especially when all this evidence is considered collectively, it is more than sufficient to establish a reasonable correlation between the proteins encoded by the claimed nucleic acids and the asserted role of the proteins as adhesive elements that bridge the RPE-retina interface, thereby making the claimed nucleic acids useful in various diagnostic and/or treatment methods. Moreover, this evidence, when considered as a whole, is sufficient to lead "a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true" (MPEP 2107.02; emphasis added). This is all the law requires. So for the foregoing reasons alone, the specification sets forth a credible utility.

Applicants nonetheless note that the Office Action fails to address whether the use of the asserted nucleic acids as part of a nucleic acid array is a credible utility. A wide variety of polynucleotide arrays are commercially available and have been widely used by the skilled persons in the art. Such arrays typically contain oligonucleotide or cDNA probes to allow detection of large numbers of mRNAs within a mixture. They are often used to study differential gene expression and to analyze candidate drugs for roles in modulation of a disease state.

Thus, it would have been apparent to one of ordinary skill in the art that the currently claimed polynucleotides are useful for inclusion on a polynucleotide array (e.g., an Affymetrix GeneChip™ array or the like) together with probes containing a variety of other genes. With increased diversity of probe sequences, the modified arrays provide improved tools

for the various applications of polynucleotide arrays. Such improved arrays are particularly useful in analyzing ocular tissues or cells. The IPMC polynucleotide sequences can also be combined with nucleic acids from other genes having roles in ocular diseases or disorders (e.g., as described in the subject specification) in an array that are specifically designed for analyzing ocular disease related gene expression. Such arrays are useful for analyzing and diagnosing cells in ocular diseases such as retinal detachment. The arrays are also useful for analyzing candidate drugs for roles in modulation of an ocular disease state (see, e.g., paragraph 90). No one would doubt that such applications of the present invention are credible.

Because the asserted utilities for the claimed nucleic acids are specific, substantial and credible for all the foregoing reasons, Applicants submit that the presently claimed invention satisfies the requirements of 35 U.S.C. 101. Therefore, it is requested that the rejections under 35 U.S.C. §§ 101 and 112 be withdrawn.

VI. Claim Rejections under 35 U.S.C. §102

Claims 1-3, 10 and 11 are rejected under 35 U.S.C. §102(b) as being anticipated by Bonaldo et al. (1996), which is said to discuss a nucleic acid having 100% sequence identity to the currently claimed nucleic acids over a region spanning 558 bases.

In response, Applicants note that the claim 1 has been amended to state that the polynucleotide comprises a nucleic acid segment or its complement, wherein said nucleic acid segment hybridizes to at least 750 contiguous nucleotides of SEQ ID NO:1 at 5 °C to 25 °C below Tm in aqueous solution at 1 M NaCl. Claim 2 has been amended to state that the polynucleotide comprises a nucleotide sequence of at least 750 contiguous nucleotides of SEQ ID NO:1. Bonaldo neither teaches or suggests polynucleotides with these sequence characteristics and thus fails to anticipate or render obvious the polynucleotides set forth in these claims.

Applicants disagree that Bonaldo anticipates claim 3, because Bonaldo fails to teach or suggest a polynucleotide that comprises SEQ ID NO:1.

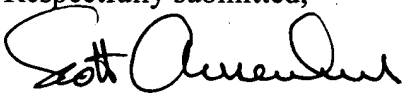
Claim 4 has been amended to state that claimed polynucleotide comprises a nucleotide sequence that encodes a polypeptide comprising at least 190 contiguous amino acids of SEQ ID NO:2. Bonaldo neither teaches nor suggests polynucleotides with these sequence characteristics and thus fails to anticipate this claim or render it obvious.

VII. Information Disclosure Statement

Applicants note that they did not receive a marked off copy of the information disclosure statements mailed on January 30, 2004 and February 2, 2004 showing that the documents cited in these statements had been considered by the Examiner. Applicants thus request that if the Examiner has not already done so that the cited documents be considered and that checked off copies of these two IDS's be provided with the next communication from the Office.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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